The Changing Face of Cystic Fibrosis

In a rural health clinic in South Africa, a toddler arrives with his mother. The boy is wheezing, extremely underweight, appears to have a respiratory infection, and has frequent, bulky stools. Because the toddler, who is black, exhibits similar symptoms to the vast majority of the doctor’s young patients - who arrive with pneumonia, severe malnutrition, tuberculosis, and chronic diarrhea – he is prescribed the same treatments. But unlike the other children, this baby has cystic fibrosis (CF), and the implications of this misdiagnosis are heartbreaking. According to the South African Cystic Fibrosis Health Trust, approximately 1 in every 2,800 white South African babies is born with CF, while the incidence of CF in the Indian and black South African population has been historically under-estimated. While there is no newborn screening program in South Africa, researchers have identified CF mutations that are specific to the black population there, which may lead to the identification of a far larger number of CF patients. This genetic detective work is currently being conducted around the globe.

While CF has long been perceived as a disease primarily affecting those of European descent, researchers in Latin America, Africa, the Middle East and Asia have

Theta Defensins: A Potential Therapeutic Approach to Treatment of Airway Infection & Inflammation in CF

By Paul Beringer, Pharm.D., Tim Bensman, Pharm.D., Ph.D. and Michael Selsted, M.D., Ph.D.

Lung disease, characterized by a chronic cycle of infection, inflammation, and obstruction, remains a key therapeutic challenge in patients with cystic fibrosis (CF). Infections with Pseudomonas aeruginosa begin early in life, with activation of the immune system to eradicate the bacteria from the airways occurring in parallel. White blood cells (e.g. neutrophils and macrophages) are a key component of the immune system and serve as early responders to combat bacterial infection (Figure 1, page 12). The body has specific molecules present on the surface of macrophages and airway cells (airway epithelium) that recognize the presence of bacteria in the lungs. Once the bacteria are recognized, these cells release alarm signals (TNF, CXCL-8) designed to activate the immune system to fight off the infection. In particular, CXCL-8 is critically important because it

Paul Beringer, Pharm.D.

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Notes from our Executive Director – Summer 2013

CFRI is standing strong today. Not only are we financially stable, we are growing in spite of a continued time of national economic duress. We now join the ranks of “medium-sized” organizations rather than small, as our budget crossed the $1 million mark!

We are recognized for our high integrity and transparency. Within the past month, CFRI has again been acknowledged by Great Nonprofits as “Top Rated.” CFRI is one of few nonprofits of our size nationally that keeps its administrative costs to a minimum and spends such a large percentage of our funds on programs.

The critical research that we support often opens new doors for medical and research communities. Our review process is run at the highest professional level, and CFRI often fits like a puzzle piece with larger funders, sending forward the best new science.

Our niche in the national CF community is clear. Through our programs and our literature, we provide information about the most current products and treatments available. The upcoming 26th Annual National CF Family Education Conference presents a variety of topics – from the CF pipeline to health insurance in 2014. Scholarships are available, thanks to our generous benefactors and sponsors. With their help, this is offered at low cost to our attendees.

Still, not everyone can be present at our events. Our CF Discovery Series was the first interactive live-streaming program of its kind in the national cystic fibrosis community. People around the world can access the Discovery Series and ask questions in real time of our presenters. This information is made available online to access at any time.

Through our ambassador program, we are increasing our presence across the country at education days, on parent advisory boards and even on transit systems! Our new bus signs are now on SamTrans and Caltrain, spreading CF awareness (see page 9).

We have an intelligent mail code (which reduces our cost and speeds the mail), QR codes for your smart phones and a new phone line: 855.CFRI.NOW. Follow us on our Facebook sites and Twitter, and through our informative newsletters, emails and dynamic website.

On August 5th, the 29th annual CF Benefit Golf Tournament will be held for its second year at the historic top 100 course, Pasatiempo Golf Club in Santa Cruz. What an outstanding opportunity to have a lot of fun in beautiful surroundings – and make an important contribution to CFRI.

As you know, our Mothers’ Day Tea is the source of a large part of our revenues. To date, we are speeding towards our goal of $205,000. Thank you to everyone who has made a donation to the Tea, especially to our Tea Senders. It is never too late to send in a donation, and we ask you to help us increase the critical research we fund and the education we provide.

We are grateful to our community for your support. Because of you, CFRI is standing strong.

Warmly,

Carroll Jenkins
Executive Director
identified numerous mutations that may completely alter previous beliefs about ethnicity and disease prevalence.

There are over 1,800 known mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) protein that cause CF. While newborn screening in the United States tests for only the most common mutations, it has nonetheless led to the diagnosis of CF in populations rarely associated with the disease, and has inspired researchers to explore the prevalence of CF mutations in these peoples’ countries of origin. According to Cystic Fibrosis Worldwide, based on the incidence of CF among Indian and Pakistani immigrants in the United Kingdom and the United States, researchers now hypothesize that India may hold the largest population of people with CF in the world, with up to 100,000 currently undiagnosed patients. While the clinical presentation of the disease in Indians is similar to those of European descent, researchers report that, “CF in Indian children is usually diagnosed late and in advanced stage,” and that, “management of CF in India is difficult,” due to a low number of specialists, limited access to healthcare, and the high cost of CF-related medications. In an article in the online IndUS Business Journal, Dr. Raju Khubchandani, a Mumbai pediatrician with a specialty in pulmonology, noted that because CF is perceived to be rare, physicians are slow to diagnose the disease. Said Khubchandani, “It’s kind of a vicious cycle. What your mind does not know, your eye does not see.”

Saritha and Sanjeev Bode’s daughter, Neha, was diagnosed with CF at 12 years old. Having emigrated from India to California, and then to Texas, the Bodes visited a wide range of doctors through the years who tested Neha for allergies and treated her for asthma. Until an allergist suggested that she have blood and sweat chloride testing, CF was never considered as a diagnosis, likely due to its perceived rarity in the Indian population. Without prior knowledge of CF, the Bodes had hoped a surgery or procedure could cure Neha, but when they went online to find answers, “it was devastating and scary,” says Sanjeev Bode. He added that the family had been trying to relocate to India at the time of his daughter’s diagnosis, but in light of the greater understanding and more advanced treatment of CF in the U.S., they decided to stay. Neha is now 16. The Bodes travel back to India regularly for business and to visit family, and are dismayed by the lack of awareness of the disease there. “I personally know five families in India whose children have CF,” says Sanjeev. “The disease is really not known in society, and it isolates the children, even impacting their chances to get married, because other people think that they are contagious.” It is very common for people with CF in India to be misdiagnosed with tuberculosis, thereby adding to the stigma, and leaving the CF untreated.

The most common CFTR mutation is delta F508, which researchers believe accounts for 66% of the CF mutations worldwide. Delta F508 is often identified with the most severe disease expression, and is found frequently in northern European CF patients, as well as in specific Middle Eastern ethnicities. Genetic researchers investigating the origins of the five most common CF mutations found that the Baluch population, an ethnic group that now resides in an area encompassing parts of Pakistan, Iran, and Afghanistan, has among the highest frequency of delta F508. Haplotype (a set of genetic determinants located on a single chromosome) studies indicate that the mutation originated between 11,000 and 34,000 years ago. While further research is required, it is highly possible that the genetic origins of delta F508 are in the Middle East, and that the mutation later spread to Europe.

Cystic fibrosis is relatively rare in Asian populations. While 1 in 2,500 Caucasians will be diagnosed, the rate for all Asians is 1 in 35,000. In China, between the years of 1974 and 2003, only 20 cases of CF were identified. In Japan, the incidence of CF is only 1 in 350,000. While rare, it does occur, but is likely to be misdiagnosed. Despite Japan’s advanced health care system, those with CF in Japan lack access to necessary medications, and their median life expectancy is approximately 15 years. Research into CFTR mutations shows that delta F508 is rare among Asian patients with CF. Disease expression may also be unique to the population. For example, in Japan, CF patients have higher rates of meconium ileus than Caucasians with CF.

For years, African Americans diagnosed with CF were assumed to have European ancestry in their family tree. With the advent of genetic analysis, African Americans with CF have been found to have mutations that are unique from those generally found in patients of European descent. In particular, the 3120+1G-->A mutation has been consistently identified in both black South African and African American CF patients. Researchers at the South African Institute for Medical
Gianna Altano lost her battle with cystic fibrosis (CF) on March 17th of this year, one day after her 23rd birthday. Her last weeks of life were spent in Stanford Medical Center’s intensive care unit in a race with time, waiting for lungs that never materialized. For her family and friends, the tragedy of her death was intensified by the thought that Gianna might have survived if more people had registered as organ donors. In a supreme act of selflessness, Danny and Sydney Altano honored their daughter’s personal commitment to organ donation and today, Gianna lives on in others who received her organs and tissue. In death, Gianna gave life.

Are you a donor? According to the U.S. Department of Health and Human Services, a person is added to the transplant list every 10 minutes. Each day, while an average of 79 people receive a transplant, 18 people die waiting, due to a shortage of organs. Donate Life America, whose vision is, “A nation that embraces organ, eye and tissue donation as a fundamental human responsibility,” notes that there are nearly 120,000 people – from infants to grandparents – currently needing organ transplants in the U.S.

By the time Anna Modlin was 29, cystic fibrosis had ravaged her lungs, leaving her dependent on oxygen and struggling to breathe. She waited nearly four months to receive a double lung transplant. Says Anna, “Before the transplant, my life was consumed simply with survival. At the end, CF took away my personality and potential. My beautiful donor saved my life. Not only with new lungs, but by giving me back my potential and letting my personality shine again. I live my life vibrantly and fully, living for the both of us, always with immense gratitude for her selfless gift.”

It is extraordinarily easy to become an organ donor. Most people register when they are renewing their drivers’ licenses, and every state has an online registry. Most importantly, people should express their wish to be a donor to their family, friends, and physicians and include their wishes in an advance directive or will.

There are many misconceptions that prevent people from becoming donors. According to Donate Life America, religion is usually not an issue, as all major religious groups in the U.S. support organ donation as, “a final act of love and generosity toward others.” Individual funeral traditions can be maintained, including services with an open casket. Do you think that you are too old to be a donor? The Department of Health and Human Services notes that a third of the deceased donors in 2011 were over 50 years old, and of these, nearly 600 were over the age of 65.

The shortage of available organs is most severe for ethnic minorities in the United States. While organs can be donated across ethnic groups, blood types and tissue markers tend to be more compatible within groups. There are many campaigns being waged to raise awareness of organ donation in these communities, and their success will translate to increased transplant opportunities for all.

During a time of unspeakable grief, many families are honoring the lives of their loved ones by giving the gift of life. As Sydney Altano, Gianna’s mother, movingly shares, “Organ donation was the right – and only – thing to do. Gianna would love knowing that she saved someone else with her kidneys, or that she helped someone to see with her corneas. It has been quite an experience being on both sides of transplant – waiting in vain as a recipient, and then as a donor family. I hope Gianna will inspire people to do the right thing and sign up as donors. In the most difficult of times, there is no greater gift.”

For more information about organ donation, go to: http://www.organdonor.gov/ http://donatelife.net/

Paradise
Step onto the beach
Feel the sun on your skin
Smell the ocean breeze
Hear the waves crashing in
See the beauty that surrounds you
And look where we live
Enjoy every moment
And try to understand what a miracle this all is

By Gianna Rose Altano
High Merit Poem
Young Poets Speak Out 2006
Getting in Tune with CF Today: Latest Research and Best Practices

August 2-4, 2013
Sofitel San Francisco Bay
Redwood City, CA

26th National Cystic Fibrosis Family Education Conference

The Top Ten: My Prescriptions for Healthy Adulthood in CF
Moira Aitken, M.D.
University of Washington Medical Center

Successfully Hitting the High Note with CF
Jerry Cahill, CF Ambassador
Boomer Esiason Foundation

The CF Therapeutic Pipeline: Kalydeco and Beyond
Patrick Flume, M.D.
The Medical University of South Carolina

Breathing Easier: New Advances in Treating CF Sinusitis
Peter Hwang, M.D.
Stanford School of Medicine

Quality of Life: Finding Balance in Your Family
Mark Pian, M.D.
University of California, San Diego

A Conversation About ObamaCare: Preparing for Change
Sherri Sager, Chief Government Relations Officer
Lucile Packard Children’s Hospital at Stanford

Should We Live in a Bubble? Best Practices in CF Infection Control
Katherine Y. Yang, Pharm.D., M.P.H.
University of California, San Francisco

How to Take Care of Your CF Gut
Elizabeth Yen, M.D.
University of California San Francisco Benioff Children’s Hospital

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CFRI Research Presentations
“Ask the Experts” Panel Discussion and Q&A
Support Groups and More

Registration before or on 7/1/13 - $175 per person (includes meals)
Registration after 7/1/13 - $210 per person (includes meals)
Limited scholarships available to eligible applicants.
Register early at www.CFRI.org or call 1.855.CFRI.NOW toll free.
The Gift of Story Telling

By Olin Dodson

W
hen my daughter passed away from cystic fibrosis in 1997, it felt like my life ended. Melissa was only 18. I had known her for just 7 years – and that’s a long story – but we had a wondrous life together. Her abrupt passing, on top of her continuous struggles and hospitalizations, left me bereft and despondent.

It took nearly seven more years before I found an interest in living once again. One of my greatest problems in those days and nights of darkness was the sense that each passing day was taking me further away from the Melissa I knew and loved. I feared that the experience of looking into her deep eyes and cradling her hand would become a faded memory. I existed under the power of two ideas: a) grief never ends; and b) you must let go and get on with your life. I was fortunate to learn that those two hope-shredding ideas were incomplete. Fully formed, they are: grief never ends, but love never dies; and let go in incomplete. Fully formed, they are: grief never ends, but love never dies; and let go.

Thomas Attig, in his book, How We Grieve, describes loving in absence as a desirable activity. He writes that, through story-telling, “we maintain a living relationship with our deceased loved one, one in which we allow ourselves to be transformed by the gift of the other’s life. Searching for lasting love in separation is our best hope for transcending suffering and reaffirming the continuing meanings of the life now ended and of our own.”

After Melissa died, as I wrote the story of our years together, I soon discovered that she was with me every day. And, four years later, when I finished the book, Melissa’s Gift, I realized that I had not let go of Melissa; she was closer and more real to me than she had ever been. I saw her face and talked to her. I detected her handprint in different places in my life. I got on with my life with her. Melissa’s presence with me grew through my process of re-engaging with her in my imagination and writing, and delving deeply into the details of our love and sorrow.

Once I found a publisher for Melissa’s Gift, I studied contemporary thought about grief and loss. I began teaching workshops on grief, mixing the insights from my studies with conversations, dreams, and stories from life with my daughter. With each telling of stories, we continue to experience the love for – and from – the one we lost.

The stories, dreams, ceremonies and honoring of those who have passed enrich us. Together, we are part of a subculture of people who seek to fully embrace life in all of its joys and sorrows and see no point in merely “moving on” from loss. In our differing ways we let go, but allow ourselves to be continually touched and influenced by a love which never ends, and the person who is so, so dear to us.

Olin Dodson is the author of Melissa’s Gift, Bay Tree Publishing.

Thomas Attig is the author of How We Grieve, Oxford University Press.

The Changing Face of CF (continued from page 3)

Research and the University of the Witwatersrand in Johannesburg observed that the 3120+1G-->A mutation has also been found in Saudi Arabians and Greeks, and hypothesized that the mutation originated in Africa and then “spread to other parts of the world via slave trade routes.” This theory is supported by CFTR mutation testing in Latin America, where the 3120+1G-->A mutation has been found in those of African ancestry. The researchers also noted that based on their understanding of CF mutations in the black South African population, they would expect at least 172 black babies born with CF in the nation each year. Yet only a handful of cases are diagnosed annually – likely due to misdiagnosis because of the perceived rarity of the disease in that population, and the fact that, “In countries where the infant mortality rate is high, the number of deaths from CF may be small in comparison to other causes.”

The high infant mortality rates found in many nations complicate the ability of physicians to diagnose cystic fibrosis. Between the lack of newborn screening, few facilities to conduct genetic analysis, lack of access to healthcare, and little awareness of the disease, it is highly likely that numerous children are struggling due to undiagnosed CF. This is the case in much of Latin America. The Caribbean and Latin America are extremely heterogeneous, including people of Amerindian, European, African and Asian descent. Researchers analyzed CF mutation data from 10 Latin American countries, and found a wide distribution of 89 mutations. Countries with large concentrations of people of European ancestry had high rates of delta F508. Countries with a high percentage of Mestizo residents, defined by the researchers as, “a highly admixed population between Europeans (mainly Spaniards), Amerindians and, in some regions, Afrodescendants,” had a far broader range of mutations.

Awareness of the disease among medical professionals and the general population varies dramatically by country. In Argentina, FIPAN (a CF organization similar to

(continued on page 7)
CF Awareness Day
A Global Event!
September 8, 2013

CF Worldwide (CFW) has long recognized that there are many faces of cystic fibrosis (CF): it is a global disease. Undiagnosed or under-diagnosed in most countries, CF takes a high toll and reduces the lifespan for many to less than ten years.

To spread information and education about cystic fibrosis and improve the lives of those who have the disease, CF Worldwide has declared September 8th as a globally acknowledged Worldwide CF Day.

On that day, CFRI joins the international CF community in bringing light to the need for CF care around the world. We advocate for the minimum basic standards of care in all countries. Our website provides current CF information and our streamed productions offer the opportunity to dialogue with experts about this disease across the globe.

The benefits of newborn screening are clear, as many children who may have been previously misdiagnosed because they did not fit the ethnic profile for the disease will now receive the early intervention that is key to positive health outcomes. Cystic fibrosis has historically been seen as a disease primarily affecting those of European descent, but this perception is no longer accurate. Newborn screening and global research into CFTR mutations is rapidly changing the face of the cystic fibrosis population.

We applaud CFW for shining the spotlight on the global need for basic care of cystic fibrosis. Following New Zealand’s lead, we will be distributing bubbles as well as free “Worldwide CF Day” tee shirts at our Conference to spread CF awareness on September 8. And we encourage everyone to sign the Worldwide CF Declaration. For more details, visit CFW at www.worldwidecfday.org

The Changing Face of CF (continued from page 6)

CFRI estimates that there are 300 to 400 babies born each year with CF, but only 5% of the cases are detected. In Mexico, where the current life expectancy for those with CF is only 17 years, it is estimated that of the projected 300 babies born with the disease each year, only 15% are diagnosed. Guadalupe Campoy, director of the Asociación Mexicana de Fibrosis Quística AC (Mexican Cystic Fibrosis Association) says, “It is an illness that, in Mexico, the doctors do not know how to detect nor to treat, for which there is no infrastructure for diagnosis or care, which becomes a heavy physical, economic and emotional weight for patients and their families.”

Due to the myriad issues that complicate cystic fibrosis screening and diagnosis in much of the world, the exact number of CF cases remains a statistical guessing game. Every state in the U.S. now has a newborn screening program, and because of the country’s large and heterogeneous population, the results of these screening programs provide valuable information about the prevalence of cystic fibrosis in diverse communities. In California, data from the first five years of newborn screening reveals that 45% of diagnosed babies were Non-Hispanic White, 43% were Hispanic, 6% were Non-Hispanic Black, and Asian/other ethnicities accounted for the remaining 6%. The ethnic make-up of the newly diagnosed babies has taken many CF centers by surprise, and they have been challenged to provide adequate information to the patients and families in their native language.

At the Cystic Fibrosis Center at Lucile Packard Children’s Hospital at Stanford, California, over half of the patients diagnosed with CF since the implementation of newborn screening are Hispanic, and multiple ethnicities are represented in their patient population, with a wide variety of mutations. In addition to language and cultural considerations, due to the variance in mutations, some babies are diagnosed with CF who have no overt signs of the disease, and it can be challenging for clinician staff to convince families of the importance of immediate and consistent treatment. Says Jackie Zirbes, DNP, RN, primary clinician for the CF center’s newborn program, “The presentation of CF features are affected by CFTR genotype as well as by other genetic and environmental factors. One of the greatest challenges is providing counseling, and determining the degree of treatment for those infants who present with CFTR changes with uncertain or unknown clinical significance. Striking a balance between early intervention and prevention for those infants with non-classic cystic fibrosis continues to be a challenge, as we know that CFTR genotype does not accurately predict individual outcome.”

The benefits of newborn screening are clear, as many children who may have been previously misdiagnosed because they did not fit the ethnic profile for the disease will now receive the early intervention that is key to positive health outcomes. Cystic fibrosis has historically been seen as a disease primarily affecting those of European descent, but this perception is no longer accurate. Newborn screening and global research into CFTR mutations is rapidly changing the face of the cystic fibrosis population.
The following is an update on three drugs in development for the treatment of cystic fibrosis, which have previously appeared in CFRnews.

Ataluren

With $60 million of new funding under its belt, PTC Therapeutics, Inc. is poised to move forward with its clinical development of Ataluren, an investigational new drug for the treatment of patients with nonsense mutations in cystic fibrosis (CF) and Duchenne muscular dystrophy. This infusion enables PTC Therapeutics to continue to pursue regulatory approval, as well as to support a Phase 3 confirmatory trial, with the goal of enrolling participants in the first half of 2013. “This financing is critical to expanding our efforts to develop and commercialize novel therapies that may benefit patients with nonsense mutation Duchenne muscular dystrophy and cystic fibrosis,” according to Stuart Peltz, Ph.D. and Chief Executive Officer of PTC Therapeutics, Inc.

Ataluren, formerly known as PTC-124, is an oral drug designed to restore the production and enable the formation of a functioning protein in CF patients who have what is known as a “nonsense” or “stop” mutation. Approximately 10% of people with cystic fibrosis have nonsense mutations, which interrupt the production of the cystic fibrosis transmembrane regulator (CFTR), thereby halting the synthesis of this essential protein.

Past studies of Ataluren in children and teens with nonsense mutation cystic fibrosis (nmCF) show that treatment with Ataluren improved lung function, reduced coughing and resulted in statistically significant improvements in the production and function of CFTR. It is pharmacologically active and generally well tolerated in children and teens.

Bronchitol

Bronchitol, an effective treatment to clear mucus from the lungs of people with cystic fibrosis, developed by Pharmaxis, received regulatory approval from the European Medicines Agency and is being used in a number of countries including Australia, Germany, Austria, Denmark and the United Kingdom, and will be available soon in other parts of Europe. Pharmaxis also recently completed plans to bring Bronchitol to Brazil in the near future.

Bronchitol is an inhalable dry-powder mannitol (a sugar alcohol) and osmotic agent, which increases mucociliary clearance. Once inhaled, Bronchitol’s dynamic mode of action on mucus reduces its viscosity and enhances airway clearance. Among its other desirable features is the ease of administration using a simple, disposable, capsule-based dry powder inhaler without the need for refrigeration, nebulization, equipment cleaning, or sterilization.

As for Bronchitol’s availability in the United States, after receiving supportive testimony from CF physicians, patients and organizational leaders in January 2013, and reviewing data gathered from two large Phase 3 clinical trials, the United States Food and Drug Administration’s (FDA) Pulmonary-Allergy Drugs Advisory Committee ruled that the statistics regarding efficacy and safety failed to provide enough evidence to approve Bronchitol, at least at that time. Pharmaxis is currently working with the FDA to identify additional clinical data that will support the resubmission of their application for Bronchitol in order to gain approval. “Despite recent setbacks in getting Bronchitol to patients in the United States,” Stephen Beckman, President of Pharmaxis, said assuredly, “we’re not giving up and will pursue all appropriate means to achieve regulatory approval so that Bronchitol can help patients living with cystic fibrosis.”

Kalydeco and VX-661

Data from a Phase 2 study of VX-661 in combination with Kalydeco was published in late April showing significant improvements in lung function among adult cystic fibrosis patients who have two copies of the most common CF mutation, delta F508. The study enrolled 128 people with CF ages 18 and older, and evaluated four dose levels (10, 30, 100, and 150 mg) of VX-661 dosed once daily for 28 days in combination with Kalydeco (150 mg) dosed twice daily. The study also monitored a separate group of patients who received VX-661 without Kalydeco for 28 days. The primary endpoints of the study were safety, tolerability and change in sweat chloride. The secondary endpoint was change in lung function. Results showed that those who received the two highest doses of VX-661 in combination with Kalydeco had the greatest improvement in lung function, but improvements were observed in all the combination dosing groups.

Cystic fibrosis is caused by a defective or missing cystic fibrosis transmembrane regulator (CFTR) protein resulting from mutations in the CFTR gene. In people with two copies of the delta F508 mutation, little to no CFTR reaches the cell surface and VX-661, known as a “corrector” is believed to help correct this problem. Kalydeco, a “potentiator,” keeps cell surface protein channels open longer to increase the flow of salt and water. Worldwide, nearly half of people with cystic fibrosis have two copies of the delta F508 mutation, and an additional one-third have one copy of the delta F508 mutation.

The data from this first study of VX-661 and Kalydeco “provides further validation of the strategy of using a corrector and a potentiator to improve lung function in people with the most common type of cystic fibrosis,” explained Peter Mueller, Ph.D. and Chief Scientific Officer and Executive Vice President of Global Research and Development at Vertex.
At the center of every cystic fibrosis (CF) care team is the patient. During her presentation, “Your CF Pharmacist: A Critical Member of the Healthcare Team,” Kathy Yang, Pharm.D., M.P.H., Infectious Disease Pharmacist and Associate Clinical Professor at University of California, San Francisco’s School of Pharmacy, spoke directly to those with CF and stressed, “You are the driver of your health care. Your job is to stay the most informed about your care, and to make sure that every member of your team knows everything they need to know about you.”

While the word “pharmacist” often conjures the image of a person filling bottles with pills, this notion is outdated, said Dr. Yang, as today’s pharmacists are “experts on medication management.” They “identify, prevent and resolve drug-related problems, encourage proper use of medications, and provide general health promotion and education.” She added, “Pharmacists are a great resource for information.”

As CF progresses, the patient’s treatment load intensifies. Unfortunately, non-adherence increases with age and disease severity, most often due to a lack of time. Dr. Yang noted, “This is where having a good, open dialogue with all your health care providers – and especially your pharmacist – can help you to work your treatments into your lifestyle, not your lifestyle into your treatments.”

While 82% of American adults take at least 1 medication, 29% take 5 or more. For those with CF, the number of medications usually far exceeds this. There are over 700,000 emergency room visits, and 120,000 hospitalizations per year due to medication adverse events, many of which are preventable. Pharmacists seek to play a key role in reducing the risk of these adverse events.

What is the patient’s role? Dr. Yang stressed that patients should ask questions, use the same pharmacy for all prescriptions, and make sure the pharmacy has a complete profile of their medications, including over-the-counter drugs and herbal supplements. It is extremely important that patients bring an accurate and up-to-date medication list to all medical visits to review with all care providers. She urged people to find a system that works for them, whether it is carrying a print-out, using a flash drive, or putting the list on one’s smart phone.

“Transition of care,” in which patients move between care settings (home, hospital, clinic) or care providers, “is a really hot topic in medicine,” said Dr. Yang, because 40% of all medication errors occur at this time. Pharmacists should be integrated into all phases of patient care to prevent problems. Key to this is a “medication reconciliation,” in which medication orders are compared to all drugs that a patient is taking so as to avoid “inconsistencies, omissions, duplications, incorrect drugs, and dosing errors.”

Infectious disease pharmacists address physicians’ questions regarding patients’ CF-related culture results which show drug resistance or allergies, and help to find the best treatment options. Home care pharmacists serve as a resource for questions related to home IVs, respiratory and enteral therapy. Community pharmacists play a very important role, said Dr. Yang. “They are by far the most accessible health care practitioners in the community, and are a wealth of medical information.”

Dr. Yang shared a list of “things to know about your medications,” which included: What is the medication for? How does it work? How am I supposed to take it? How long do I take it? Should I take it with/without food? What are the side effects? Where do I go for information if I have questions? Are there interactions with other drugs, dietary or herbal supplements? What activities should I avoid? What if I miss a dose? How should it be stored? Patients should be able to answer all of these questions for optimal impact.

Dr. Yang concluded by using a waterfall as a metaphor for the public health system, “which is currently set up to fish people out of the water at the bottom and to treat them for injuries.” Dr. Yang encouraged everyone to be educated and active members of their care team, because, “It is better to figure out what the problem is while still above the falls.”

May was CF Awareness Month, and CFRI posters on Caltrain and SamTrans buses helped to spread awareness to commuters and tourists in the San Francisco Bay area. Working in collaboration with non-profits, providers, clinics, researchers and caregivers, CFRI connects CF resources with community needs. Learn more on our website: www.CFRI.org.
A lthough many related health issues occur in patients with cystic fibrosis (CF), the concerns of oral hygiene and CF are rarely mentioned. There are few research articles regarding this topic, especially in comparison to other CF-related subjects. One useful resource is a 2010 publication by the College of Dental Hygienists of Ontario (CDHO), titled “CDHO Advisory: Cystic Fibrosis.” This overview describes how CF is expressed, its treatments and medications, medication side effects and comorbidity, as well as complications and conditions related to oral health.

Dr. Tabreena Walker, D.D.S., of Harker Heights, Texas, has published additional information regarding dental health, including CF, on her website. She states that patients with cystic fibrosis should try to schedule dental appointments when their airways are most clear, and bring their inhalers to dental visits. The textbook, *Pediatric Dentistry: A Clinical Approach, Second Edition*, emphasizes that the high flow of gases, such as oxygen or nitrous oxide used during dental procedures, can dry out respiratory secretions and lead to further mucous plugging and infection. It suggests that a latex rubber or silicone dam be used to protect the patient’s airway from any materials, which may be inhaled during treatment.

Studies show that poor dental health is connected to major chronic diseases. “Links Between Oral Health and General Health – The Case for Action,” a report released in December 2011 by Dental Health Services, Victoria, B.C., explains the link between dental health and respiratory illness. It states that oral health issues and major diseases share common risk factors and may cause or worsen oral health conditions. On the other hand, in 2004, K.M. Johan, D.D.S., Ph.D., presented “Is Oral Health At Risk in Patients with Cystic Fibrosis?” in which he noted that CF patients appear to be protected against dental decay. He concluded that, most likely, unknown salivary components are responsible for this protection.

Articles concerning oral hygiene and CF include:

**Oral Health Risks in Patients with Cystic Fibrosis**


This study investigated the determining factors of oral health in CF homozygotes, CF heterozygotes and healthy controls. CF homozygotes had significantly lower amounts of decay, while CF heterozygotes were not significantly higher than the healthy controls. CF homozygotes also had significantly lower Streptococcus mutans counts (a significant contributor to tooth decay) than other groups and less bleeding of the gums. No significant differences in plaque and tartar amounts were found between the three groups. The influence of typical CF medications on oral health was found not to be significant. Both CF groups had significantly higher salivary sodium concentrations than controls, and CF homozygotes had a significantly higher salivary phosphate concentration than both other groups.


**Oral Health of Patients With Cystic Fibrosis and Their Siblings.**


The extent of tooth decay, oral hygiene, below the jaw gland enlargement, the manner in which the upper and lower teeth come together when the mouth is closed, incomplete dental development and staining of permanent teeth, were evaluated in 63 patients with CF who were on broad-spectrum antibiotics and digestive enzymes. The findings were compared with those of their near-aged siblings. Gland enlargement and dental staining were increased in patients with CF. While tooth decay was significantly decreased, no other significant differences were found.

http://tinyurl.com/d698f9j.

**Oral Health of Patients With Cystic Fibrosis and Their Siblings.**


This study examined the relationship between antibiotic usage and plaque, gingivitis and dental decay in children with CF. Their scores for plaque, gingivitis and decay were compared with those of healthy children. Results suggest that antibiotic therapy may be a major cause of the lower levels of dental disease.

http://tinyurl.com/c2lknu3

(continued on page 12)
Meet some great friends.

Know that you’re not alone.

Purpose of the Retreat: The retreat provides a safe and welcoming environment aimed at enhancing positive coping skills, social support and education for people who share common experiences with CF.

What We Do: Activities that promote health include: daily exercise, arts and crafts, rap sessions, and educational workshops with guest speakers. Fun group-bonding activities include a talent show, games, and “just hanging out” getting to know others.

Cost: $85 per person for the entire week. Daily fees are $15 per day for visitors or $10 per meal. Hotel and transportation fees are not included. On-site private rooms/baths are available at $55 per night. Scholarships are available.

Learn more about CF self care.

Experience a place for hope & healing.

Who Can Come: Teens and adults 15 years and older with cystic fibrosis*, their family members, friends and health care providers.

Safety: All people with CF are required to comply with CFRI’s Infection Control Policy and on-site protocols. A medical advisor is available at the Retreat. Participants with CF must obtain a sputum culture before the start of the retreat.

*People who have ever cultured Burkholderia cepacia, cultured Methicillin-resistant Staphylococcus aureus (MRSA) within the past 2 years, have had two or more consecutive positive cultures for Nontuberculous mycobacteria (NTM) in the past 12 months, or are currently resistant to all antibiotics will not be allowed to attend the retreat.
is responsible for instructing neutrophils to move into the lungs.

The influx of neutrophils into the lungs is a sign of airway inflammation. Once activated in the lungs, the neutrophils combat infection by surrounding and engulfing the bacteria (i.e. phagocytosis). One way in which the process of phagocytosis occurs in neutrophils is through CXCL-8 engagement with another specific molecule (CXCR1), resulting in cellular communication and action. Importantly, in CF, phagocytosis is impaired in part due to loss of CXCR1 molecules on neutrophils, thereby preventing phagocytosis of bacteria. Loss of the CXCR1 molecule (or protein) on neutrophils occurs as a result of the action of enzymes (proteases) released by accumulated neutrophils in the airways of patients with CF.

In addition to phagocytosis, neutrophils release antibacterial proteins designed to kill bacteria that have invaded the airways. One example is neutrophil elastase, which works by degrading key proteins necessary for bacterial survival. However, due to the large number of neutrophils in the airways in CF, neutrophil elastase (and other proteases) accumulate to very high amounts and can degrade structural proteins (e.g. elastin, fibronectin) of the lung.

Another group of proteins released by neutrophils are the antimicrobial peptides (AMPs), which include defensins, lysozyme, and lactoferrin. AMPs exhibit very broad and potent activity against many bacteria, viruses, and fungi. Recent studies have demonstrated that several of the AMPs are less active in the airways of patients with CF. The defect in the CFTR protein leads to reduced bicarbonate secretion resulting in an acidic lung fluid. The acidic environment reduces the antibacterial activity of lysozyme. In addition, lactoferrin and beta-defensins are susceptible to degradation by airway proteases. Together, the loss of AMP activity and impaired phagocytosis contribute to persistent infection and perpetuate the cycle of infection, inflammation and obstruction leading to progressive loss of lung function in CF.

The potential use of antimicrobial peptides to counter infection and inflammation in CF lungs is an attractive area for the development of new therapies. One particular group of antimicrobial peptides called the theta defensins have shown potent anti-inflammatory activity as well as antibacterial properties against a broad spectrum of bacteria, including multidrug resistant strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which are common to CF. These peptides (theta defensins) are found within neutrophils from rhesus macaques and baboons, but not in humans. Unlike AMPs produced in our neutrophils, these peptides are extraordinarily stable due to their cyclic structure. Interestingly, we have demonstrated the stability of rhesus theta defensin-1 (RTD-1) in protease rich CF sputum and acidic conditions. Moreover, RTD-1 administration has demonstrated to be highly effective in animal studies of life-threatening bacterial bloodstream infections. In addition, topical delivery of RTD-1 to the lungs protected mice from otherwise lethal effects of viral infection caused by SARS-Coronavirus.

Importantly, these studies revealed that in addition to their antibacterial activity, theta defensins also exhibit potent anti-inflammatory activity. Preliminary studies indicate the anti-inflammatory action of RTD-1 is mediated by reducing the levels of TNF, a protein that stimulates the production of CXCL-8 and the influx of neutrophils into the airways. Reducing the number of neutrophils in the airways is an important therapeutic target since high numbers of airway neutrophils are associated with more severe lung disease. We recently performed experiments in an animal model of acute neutrophilic airway inflammation, and demonstrated that RTD-1 administered under the skin reduced the number of neutrophils within the airways as the dose of RTD-1 increased. RTD-1 also inhibited proteases (e.g. MMP-9) and may therefore reduce lung damage.

Collectively, these studies demonstrate that cyclic theta defensins are promising therapeutic candidates for development as a treatment option for CF. Our lab is currently conducting animal studies designed to determine the optimal dose, safety and effectiveness of RTD-1 administered to the lungs in mouse models with CF. These studies are key to providing data necessary for translation to potential future studies in humans.

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**ORAL HEALTH (continued from page 10)**

**Oral Health and Related Factors in Cystic Fibrosis and Other Chronic Respiratory Disorders.**


According to this paper, enamel defects, particularly enamel cloudiness, are more common in CF patients. The authors suggest that long-term use of antibiotics and pancreatic enzymes may provide some protection against the development and progression of dental decay.

http://tinyurl.com/d7b4v85

**Assessment of Dental Status and Oral Hygiene in the Study Population of Cystic Fibrosis Patients in the Podlasie Province.**


The researchers state there is a serious risk of decay in CF patients due to the severe course of the disease, long-term administration of medications, and a high carbohydrate diet. They suggest that CF patients remain under constant dental care according to individually designed programs of oral health and decay prevention.

http://tinyurl.com/ckhagw4
The Mothers’ Day Tea: Then and Now

By Jane Mitchell

Picture a beautiful home, where you are sipping tea, munching on tasty treats and talking with mothers, fathers, grandparents, and fellow supporters of Cystic Fibrosis Research, Inc. (CFRI). Two of the founders, Maxine Eggerth and Elizabeth Mayer, along with Ann Robinson, one of the original members of CFRI, are beside you, reflecting on the creation of the Mothers’ Day Tea, which in its first year had a goal of raising $500, as compared to this year’s $205,000. Their “creation” has grown into CFRI’s largest fundraiser of the year. It was an honor to be invited to the Mothers’ Day Tea kick-off reception, hosted by Barbara and Jim Curry, CF grandparents, at their home in Hillsborough, CA last March.

After enjoying our tea, we went around the room sharing our experiences living with CF and then were read a letter of inspiration, written by Stacey Lawn, who expressed fond memories of helping to stuff envelopes for the Mothers’ Day Tea at her Nana’s dining room table when she was young. Her mother continued in her Nana’s tradition and now that her mother is ill, Stacey is keeping her family’s tradition alive by continuing the legacy the women in her life held so dear. The annual ritual of these mothers makes a difference in the many lives of those living with cystic fibrosis, including my own daughter Hannah. As a parent, it is a blessing to be part of an organization where education is continuous and always informative with new findings and research. Knowing that CFRI’s funding is going toward research that helps Hannah’s health and could possibly lead to a cure for CF is amazing.

As a wonderful alternative, CFRI now offers the opportunity to reach out to others online to participate in the Mothers’ Day Tea. Along with sending letters through the mail, one can also create a personalized home page and email invitations to their loved ones. For more information on becoming a Tea Sender, or creating your own personal home page for donations, please visit www.CFRI.org.

I would like to conclude by sharing an excerpt from the first Mothers’ Day Tea letter ever distributed by the Founders:

“ ’It’s a fundraising medium, true, But we hope that you’ll feel as we do, And regardless of the weather, We’ll all be together In our thoughts for an hour or two. As you sit sipping your tea, Think of the end we could see. Be you family or friend, Our CF children depend On your joining our ‘Make Believe’ Tea.’”

CFRI – New Infection Control Policy

QUESTION: Can I attend a CFRI event if I have CF?

ANSWER: It all depends on your most recent culture results!

It is a significant challenge to create an opportunity for people with CF to come together safely. At CFRI, we are committed to creating the safest environment possible at our events to minimize the risk of cross-infection. One way we do this is by requiring all attendees with CF to comply with our infection control policy, which has been revised this year.

KNOW YOUR SPUTUM CULTURE!
Scientists continue to identify specific pathogens that compromise the respiratory and digestive systems and impact other organs in those with CF. Some bacteria, such as B. cepacia, are particularly resistant to treatment and can take a major toll on health.

Therefore: (1) People with CF who have ever tested positive for B. cepacia, or (2) have had methicillin-resistant Staphylococcus aureus (MRSA) in the past two years cannot attend CFRI sponsored events. In addition, (3) anyone who has had two or more consecutive positive cultures for Nontuberculous mycobacteria (NTM) in the past 12 months or, (4) who is resistant to all antibiotics, cannot attend.

We support the unique fellowship and exchange of information that transpires when the CF community comes together—provided that our strict cross-infection standards are maintained. Check our website www.CFRI.com for a complete copy of our new infection control policy, which also details our hygiene guidelines.
Get Ready for School!

Updated Edition of CF in the Classroom

An update of CFRI’s publication, CF in the Classroom, is coming soon! Distribute this publication to teachers, school nurses and other people to help them understand the needs of your child living with cystic fibrosis.

This new edition also includes valuable information about the Individuals with Disabilities Education Act (IDEA), Individualized Education Plan (IEP), Section 504 of the Rehabilitation Act, and preparing for higher education.

To request copies, go to http://www.cfri.org/educate.shtml

Your Support Changes Lives

With Payroll Deduction And Matching Gifts - Workplace Giving Has Never Been Easier!

Many companies offer programs to designate a charity for donations through payroll deductions. Ask your employer about matching your gift.

Military Or Government Employee? Workplace Giving Opportunities Coming This Fall

CFRI is proud to be a member of workplace giving campaigns. Please note our code for each agency and sign up to support CFRI in the Fall 2013 campaign.

Donate Gifts of:
- Real Estate
- Stock
- Planned Giving
- Cars, Boats or RVs!

Need more information? Contact JoAnn Davis at jdavis@cfri.org or 650.404.9979

Combined Federal Campaign
CFC Code #76262

California State Employees Charitable Campaign
CSECC Code #12438

Community Health Charities of CA
CHCC Code #240
“In Honor of” and “In Memory of”

Our “In Honor of” and “In Memory of” pages provide the opportunity to honor a person, family, or special event or to remember a loved one.

If you want your donation to honor or remember someone special, please include the person’s name and address with your donation.

At your request, we will send an acknowledgement of your gift to the person you designate.

Mail your contributions to:
CFRI
2672 Bayshore Parkway, Suite 520,
Mountain View, CA 94043

Contributions listed here were received between February 1, 2013 and April 30, 2013

In Honor of

February 1, 2013–April 30, 2013

Chelsa Aboud
Sadie Anderson
Lucy Barnes
Rebecca Boyer
Lauren Colonna
Mary Convento
Cameron Cornell
Barbara Curvy
Ashley Davila
Michelle Davis
Stacy Dean
Gordon DeVore
Dylan Dunn
Tess Dunn
Maxine Eggerth
Grace Ehrie
Fran Eikeberg
Elyse Elconin-Goldberg
Daniel Ellett
Hayden Ellett
Sebastian Fabricius
Billy Federal
Victoria Flamenco
The Flynn Family
Ryan Foster
Jacob Fraker
Joseph Fraker
Emily and Jessica Fredrick
Mark Gerow

In Memory of

February 1, 2013–April 30, 2013

Carol Adelman
Kimberley Adelman
Marcus Adelman
Rosemary Altano
Gianna Rose Altano
Joy Amodei
Alan Aycock
Ann Baldwin
Ronald Baldwin
Anne Beltrame
Ben Bermudez
Patricia Berndt
Wendy Bosarge
Melissa Brandon
Alicia Brogle
Kenneth Cady
Sam Callaghan
Anita Cass
Sonya Chartrand
Ryan Coelho
Rachel Crocker
Neva DeVore
Connie Doerr
Bernadine Fawley
Trevor Fenn
Shane Fisher
Lillian Fredin
Jeffrey Gibson
Lucia Glenn
Isaac Goldman
Rosalyn Goldman
Joy Haessler
Cynthia Haley
Virgil Hanson
Warren Harden
Frances Heagney
Leslie Hotson
Sean Hyland
Linda Jengo
Edward Jensen
Peter Judge
Kathy Judge Morse
Sarah Kanofsky
David Kasten
Dick Kaye
Eileen Kelly
Kurt Keonig
Bridget Klein
Raymond Kulik
Douglas Lab
Michael Lang
Elena Laughridge
Dawn Longero
Lucy Marsh
Walter McInerney
David McAfee
Lucia McLain
Jessica Mobley
Lynette Moulton
Frank Nieto
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Danny and Kevin O’Brien

Jennifer Ortman
Frank Peixoto
Sean Peterson
Irene Petrini
Catherine Rawlings
Jaimee Renfrow
Dave Ross
Billy Ruffner
Randy Rupracht
Dhea Schalles
Linda Scherschel
Heidi Schroeder
Joseph Sinnaeve
Tammy Smerber
Jamie Smolin
McDonald
Charlie Stockley
Delinda Syne
Ann Marie Thibault
Jeanne Thibault
John Thibault
Mary Ann Thibault
Patricia Thibault
Susan Thibault
Shell Trask
Marge Trask
John Trask
Linda Trojan
Dale Upton
Jennifer Uskoski
Jodi Voller
Cory Walsh
Tom Walton
Debora Ware
Haldon Weatherly
Norman Weiner
Tara Weir
Kelly Wilson
Cynthia Witman
Donald Wolter
CFRI’s Mission

Cystic Fibrosis Research, Inc. exists to fund research, to provide educational and personal support, and to spread awareness of cystic fibrosis, a life-threatening genetic disease.

CFRI’s Vision

As we work to find a cure for cystic fibrosis, CFRI envisions informing, engaging and empowering the CF community to help all who have this challenging disease attain the highest possible quality of life.